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International Journal of Current Research
Vol. 10, Issue, 08, pp.72519-72524, August, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A COMPARATIVE STUDY OF TWO DIFFERENT BRANDS OF LITHIUM CARBONATE IN PATIENTS OF BIPOLAR DISORDER

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ARTICLE INFO

Article History:
Received 19th May, 2018
Received in revised form
20th June, 2018
Accepted 27th July, 2018
Published online 30th August, 2018

Key Words:

Bipolar mood disorder,
Young Mania Rating Scale,
Lithium carbonate,
Therapeutic drug monitoring

Abbreviations:

ADR- Adverse drug reaction
BA/BE - Bioavailability/Bioequivalence
CRF - Case record form
FDA - Food and drug administration
YMRS - Young mania rating scale

ABSTRACT

Objectives: To study the relation between efficacy, safety and plasma concentration of two different brands of lithium carbonate in patients of bipolar disorder.

Materials and methods: This prospective, interventional study was done in newly diagnosed patients of bipolar disorder and randomized into two groups, Group A (generic) and Group B (branded generic).Lithium carbonate 300 mg thrice a day given orally in both groups. Data was recorded in pre validated Case Record Form. The Young Mania Rating Scale (YMRS) was measured at baseline and after 3 weeks of therapy. Serum lithium level was carried out on 21st day of therapy. Pearson Parametric Correlation Test and't' test was used for analysis.

Results: YMRS was 28 ± 1.07 and 29.08 ± 1.12 (baseline)and 14.04 ± 0.67and 14 ± 0.68(after 3 weeks) in groups A (n=25) and B (n=25) respectively. There was significant mean reduction in YMRS at 2nd follow-up (P< 0.0001). At the end of 3 weeks, the mean serum lithium level in group A and B was 0.68 ± 0.04 and 0.82 ± 0.07 respectively. One patient in each group A and B had low serum lithium level (0.2, 0.26) while 4 patients in group B had high serum lithium level (1.32, 1.32, 1.88 and 1.35). High S. lithium level was associated with increases ADRs. Correlation was significant between increases in lithium level and decrease in YMRS.

Conclusions: There is **s**trong correlation between efficacy (YMRS score), and ADRs in both generic and branded lithium carbonate.

Citation: ***Panchal, K.M., Patel, P.P., Gandhi, A.M., Chauhan, A.P. and Desai, M.K.*, 2018.** "A comparative study of two different brands of lithium carbonate in patients of bipolar disorder", *International Journal of Current Research*, 10, (08), 72519-72524.

INTRODUCTION

Bipolar disorder is manic-depressive disorder characterized by unpredictable swings in mood from mania (or hypomania) to depression and consists of at least one hypomanic, manic, or mixed episode. Mixed episodes represent a simultaneous mixture of depressive and manic or hypomanic manifestations. In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia (Girardi *et al.,* 2016). Bipolar disorder required mood stabilizers which can be defined as a medication that can treat either phase of bipolar disorder while not inducing or worsening the other phase or defined as an agent that can treat and prevent both manic and depressive episodes. By this definition only lithium qualifies as a true mood stabilizer (Licht, 2012). Lithium in hibit inositol phosphatases leads to inositol depletion in neurons and decreased neuronal activity and also increases the uptake of the excitatory neurotransmitter glutamate thereby reducing glutamate activity at the neuronal synapse (Hirschowitz *et al.,* 2010). Lithium carbonate is the mainstay of treatment in bipolar disorder although sodium valproate, carbamazepine, as well as second-generation antipsychotic agents also have been approved for the treatment of acute mania. Lithium carbonate is the first line drug for treatment of maniaas it controls the manic phase and also reduce the incidence of suicidal tendency in bipolar disorder (Aronson *et al.,* 1992; Jonathan *et al.,* 2011). Lithium has narrow therapeutic index and hence lower plasma level is ineffective while a small increase in the dose may cause the toxicity. Due to narrow therapeutic index, monitoring of serum lithium level is important for maximum therapeutic response and to prevent toxicity. Lithium carbonate is available in generic as well as branded generic product. Generic drugs are copies of branded drugs that have exactly the same dosage, intended use, effects, and side effects, route of administration, risks, safety, and strength as the original drug and development of a generic drug relies on the demonstration of its single-dose pharmacokinetic bioequivalence with the branded product in healthy volunteers (Meredith, 2003). In other words, their pharmacological effects are exactly the same as those of their

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DOI: https://doi.org/10.24941/ijcr.31259.08.2018

branded counterparts and generic drugs are marketed under its pharmacological name. Branded drug that has a trade name and is protected by a patent (can be produced and sold only by the company holding the patent). A branded generic is a drug that is bioequivalent to the original product, but is now marketed under another company's brand name and promoted by medical representatives to medical practitioners while nominally branded generics are same as branded generics, except that these drugs are supplied to distributors and retailers but are not promoted by medical representatives to medical practitioners (Andrade *et al.,* 2017). Absorption of lithium varies with different brands of lithium carbonate (Hirschowitz *et al.,* 2010). There may also be some inter individual variation to the biological response to a drug. This variation is due to differences in absorption, distribution, and elimination. Thus, measurement of plasma concentration of drug may help to individualize drug therapy (Aronson *et al.,* 1992). The therapeutic effect of lithium may be detectable in patients within 2 weeks, however it may be difficult to know whether the effect is optimal and whether it is attributable to the drug or to spontaneous remission (Aronson *et al.,* 1992). Thus, establishing the relationship between serum lithium level and therapeutic effect becomes important. This study has been proposed to measure the serum lithium level in patients' prescribed generic lithium carbonate and comparing it with patients who are prescribed branded generic lithium and to analyze relationship between plasma concentration and efficacy of both the products. It also aimed to study the safety of both these products.

MATERIALS AND METHODS

This was prospective, continuous and interventional study performed on adult patients of either gender aged 18-75 years and who were newly diagnosed as suffering from bipolar disorder and those who were willing to take part in this study. Institutional Ethics Committee approval and permission of Superintendent of Government Mental Hospital were taken. Patients were excluded from the study if they had major psychiatric illness co morbid with bipolar disorder, substance induced bipolar disorder, history of any other major medical or neurological disorders, pregnant female with bipolar disorder, patients receiving diuretics, steroids, angiotensinogen converting enzyme inhibitors, angiotensin II receptor antagonists and non-steroidal anti-inflammatory drugs, and nausea/vomiting/diarrhea or other conditions leading to salt/water depletion. All patients were included in the study after taking written informed consent. Patients were divided into two groups with a computer generated randomized table as Group A (n=25) and B (n=25). Group A patients received generic lithium carbonate (available at Government mental hospital) 300 mg tablet three times a day (900 -1200 mg) orally and Group B patients received branded generic lithium carbonate (purchased from Intas Pharmaceutical) 300 mg tablet three times a day (900 -1200 mg) orally. A detailed history, investigation and treatment taken were recorded in pre validated CRF. YMRS assessed on day 0 and clinical improvement was assessed by using YMRS at the end of 3 weeks by the psychiatrist (Andrade and Rao, 2017). Serum lithium level was carried on 21st day after starting the therapy. Blood sample was collected 12 h (± 30 min) after the last dose of lithium in patients who had been taking the drug in three divided dosages, and who had taken all their prescribed tablets at the scheduled hours for the previous 48 h. During lithium therapy other medications permitted were inject able or oral preparation of haloperidol, risperidone, olanzapine, lorazepam, and diazepam. Adverse events were monitored during therapy if any.

Data Analysis: Data were entered in Microsoft excel sheet and analyzed at the end of study by applying paired and unpaired t test and Pearson Parametric Correlation tests.

RESULTS

General characteristics: Total 25 patients were included in each group. Age of enrolled patient were between 18 to 75 years with mean age (Years) 34.64 ± 2.31in group A and 39.16± 2.13in group B (Mean ± SEM). The male/female ratio in group A was 1: 0.31 and in group B was 1: 0.25. According to analysis of level of education, total 7 patients [group A (5) and group B (2)] had studied above 12th standard and 40 patients [group A (19) and group B (21)] had studied up to 12th standard while only 3 patients were illiterate [group A (1) and group B (2)].

Symptoms: The patients presented with symptoms like excessive talking, sleep disturbance, elevated mood, hyperactive, aggressive, restlessness, assaultive behaviour, disorganized thought and persisted after 3rd week of lithium therapy as shown in Table 1.

Young mania rating scale: The mean reduction in YMRS from baseline to 2nd follow-up was 28.00 to 14.04 in group A and 29.08 to 14.00 in group B. The reduction in YMRS at 2nd follow-up was significant as compared to baseline (P value < 0.0001 for both group). The comparison of mean YMRS of group A (28.00 ± 1.07) and group B (29.08 ± 1.12) was not significant at baseline (P value = 0.254). Similarly at 3rd week also the difference between the YMRS of group A (14.04 ± 0.67) and group B (14.00 ± 0.68) (P value = 0.853) was not significant.

Table 1. Analysis of symptoms in both groups

Symptoms	Group A (n=25)		Group B (n=25)	
	Day 0	3rd Week	Day 0	3rd Week
excessive talking	56 %	32 %	60 %	28 %
sleep disturbance	64 %	28 %	68 %	32 %
elevated mood	72 %	24 %	64 %	28 %
hyperactive	52 %	24 %	56 %	24 %
aggressive	44 %	20 %	40 %	16 %
restlessness	48 %	32 %	40 %	20 %
assaultive behaviour	40 %	16 %	44 %	16 %
disorganized thought	40 %	24 %	36 %	20 %

Table 2. YMRS and abnormal S. lithium level

	S. Lithium (meq/L)	Pre YMRS	Post YMRS	Reduction in Score (%)
Group A	0.20 (low)	30	21	15
Group B	0.26 (low)	19	14	8.3
	1.32(high)	26	8	30
	1.32(high)	33	10	38
	1.88(high)	25	9	29.6
	1.35(high)	30	11	31.6

Table 3. ADR and S. lithium level

S. lithium level	ADR (present)	ADR (absent)	Total Patients
Normal	5	39	44
High	3	1	4
Low	0	2	2
Total	8	42	50

Table 4. Causality assessment, severity and preventability

	Suspected drugs	ADRs	S. lithium level	WHO-UMC score	Severity [9]	Preventability [10]
	Lithium	Headache	0.97	Probable	Mild	Not preventable
Group A	Lithium, lorazepam, risperidone	Confusion	1.04	Possible	Mild	Not preventable
(n=25)	Lithium	Polyuria	1.03	Probable	Mild	Probably preventable
	Lithium, olanzapine, trihexyphenidyl	Dry mouth	0.94	Possible	Mild	Probably preventable
	Lithium	Diarrhoea	1.32	Probable	Moderate	Probably preventable
	Lithium	Lethargy	1.88	Probable	Mild	Not preventable
Group B	Lithium, olanzapine, diazepam,	Muscle	0.96	Possible	Mild	Not preventable
(n=25)	trihexyphenidyl	weakness				
	Lithium	Polyuria	1.35	Probable	Mild	Probably preventable

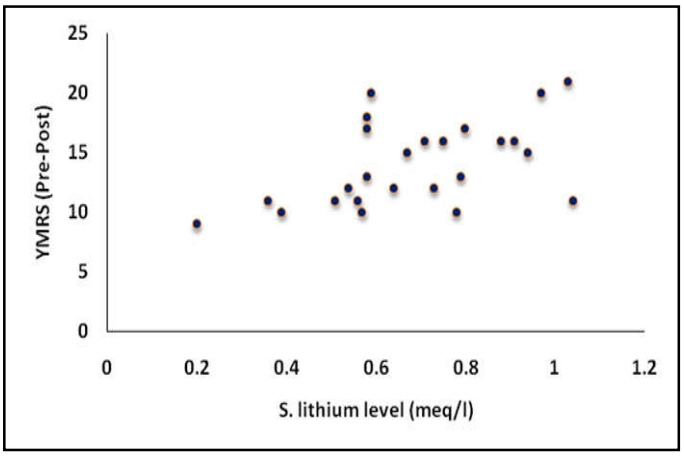

Figure 1. Correlation between S. lithium level and YMRS score in group A (n=25)

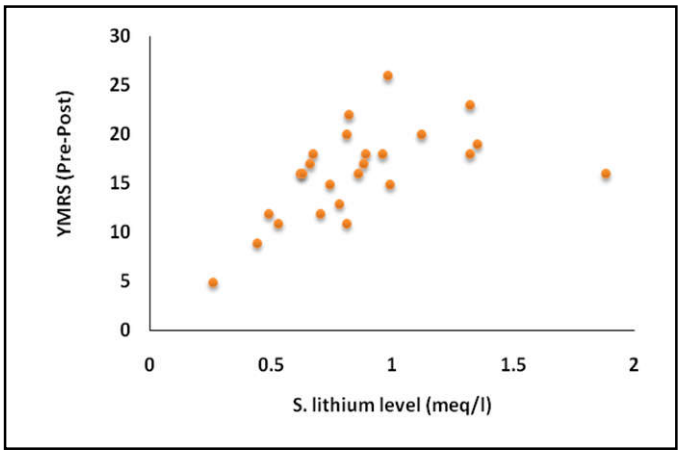

Figure 2: Correlation between S. lithium level and YMRS score in group B (n=25)

To compare the efficacy of group A and B, the mean difference was measured for each group. The difference of the baseline and 2nd follow up data was calculated. The mean difference of YMRS for group A was 14.08 ± 0.70 and for group B 15.88 ± 0.98. Mean difference for both group was compared using unpaired't' test. Mean difference of YMRS was not significant between group A and B (p=0.14).

Concomitant drug therapy: Some patients received one or more concomitant drugs as add on therapy with lithium to control the additional psychotic features and as an augmentation therapy. Drugs such as olanzapine, diazepam, trihexyphenidyl, risperidone, lorazepam, sodium valproate and clonazepam were permitted. According to analysis of concomitant drug therapy, in group A, 6 patients received trihexyphenidyl (24 %), 5 patients received diazepam (20 %), 3 patients each received risperidone, olanzapine and lorazepam (12 %) and 1 patienteach received sodium valproate and clonazepam (4 %). In group B, 10 patients received diazepam (40 %), 6 patients received trihexyphenidyl (24 %), 5 patients received risperidone (20 %), 4 patients received olanzapine (16 %), 2 patients received sodium valproate (8 %) and 1 patient received clonazepam (4 %).

Serum lithium level: At the end of 3 weeks, the mean serum lithium level in group A was 0.68 ± 0.04 and in group B was 0.82 ± 0.07. Mean difference between both group (0.1396) was not significant (P value = 0.1078) but the mean serum lithium level in group B was found little higher than in group A. Out of 25 patients in each group, 24 patients in group A and 20 patients in group B, the serum lithium level was within normal limits (0.3 to 1.2 meq/l). Four patients of group B had the serum level high i.e. > 1.2 meq/l than therapeutic level. One patient in both group A and B had serum lithium level lower than the normal therapeutic range.

YMRS and S. lithium level: In group A, 24 patients had normal S. lithium level showed 23.81 % improvement in YMRS at 3rd week while 21 patients in group B had normal S. lithium level showed 25.95 % improvement in YMRS at 3rd week. As shown in table 2, patients who had lower S. lithium level (< 0.3 meq/L) the decrease in YMRS score was lower than the 15 % reduction in YMRS score. Four patients of group B had high S. lithium level (> 1.2 meq/L) but their score also decrease equally or a little more than the average score.

Correlation between plasma lithium level and YMRS: Correlation between plasma lithium level and difference of YMRS score was done by Pearson Parametric Correlation test in both groups. Difference between baseline and 2nd follow-up YMRS score was counted in both groups. The Correlation coefficient (r) ranges from -1 to 1. A value of score greater than 0 to 1 indicates that there is a positive correlation with YMRS and plasma lithium level which indicates YMRS score improves when there is an increase in plasma lithium level within therapeutic range. Correlation coefficient (r) was found 0.5171 in group A which was significant (P value= 0.0081).Thus, YMRS score improves with increase in plasma lithium level. Correlation coefficient (r) was found 0.5851 in group B which was also significant (P value= 0.0021) and suggests that YMRS score improves with increase in plasma lithium level. Figure 2 and 3 shows correlation between S. lithium level and YMRS score in group A and B.

Adverse effect: As shown in table 3, total 16 % patients developed ADRs during lithium therapy. Four patient each in both group A&B experienced adverse drug reactions. Suspected drugs, causality assessment, severity and preventability for all adverse effects was done in both groups. Out of 8 ADRs, 3 ADRs were also suspected due to other concomitant dugs apart from lithium. WHO-UMC causality

assessment was probable in 5 patients and possible in 3 patients. Severity assessment was mild except in 1 patient. According to preventability assessment, four ADRs were probably preventable. When the ADRs were compared with the serum lithium level it was observed that 3 patients in group B had high S. lithium level than normal therapeutic range while remaining 5 patients in both group had S. lithium level within normal range. The patients who had high lithium level and developed ADR, they were only on lithium therapy. Fisher exact test was applied to analyze the S. lithium level and ADRs. The result was statistically significant (P value < 0.011) which means increase in serum lithium level is associated with increasing number of adverse effect.

DISCUSSION

Bipolar disorderis manic-depressive disorder characterized by unpredictable swings in mood from mania (or hypomania) to depression. It is also chronic, recurrent mood disorder that typically develops in adulthood and is associated with substantial morbidity, mortality and with high suicidality. Bipolar disorder is not only disabling, affecting daily functioning and leading to loss of employment, it is also relatively common and has a high rate of co-morbid medical illness that increases mortality (Kupfer, 2005; Kessler *et al.,* 2005). Acute mania is associated with substantial negative personal, interpersonal and social consequences hence effective and rapid pharmacological control of the condition is a necessity and towards this a variety of agents are available currently. They are lithium, antipsychotics, benzodiazepines, anticonvulsants like carbamazepine, valproate etc (Prakash and Bharath, 2000). Lithium carbonate is available in generic and branded generic preparation and due to narrow therapeutic index it should meet standards in context to bioequivalence and produce the same therapeutic effect and to avoid toxicity. This prospective, continuous and interventional study was carried out to compare the efficacy and safety of two different brands of lithium carbonate. Patients were divided into two groups group A (n=25) and B (n=25) using a computer generated randomization table method in which group A was prescribed generic lithium and group B was prescribed branded generic lithium. In our study, the mean age of the patients was 37.46±1.54 (Mean ± SEM) years while male/female ratio was 1: 0.31. Study done by Nisha *et al.* (2015) also showed similar mean age of the bipolar mood disorder patients (39.1±8.80) (Nisha *et al.,* 2015). Bipolar disorder mostly affect the age between 20 to 40 years because of stressful life in younger age groups. It may be due to family and marital status which appears to be one of the most consistent risk factors for bipolar disorder. Widowed, separated and divorced persons are at higher risk to develop bipolar disorder (Heim *et al.,* 2002). In our study, 80 % of the patients had lower education level (80 % of patients were studied upto 12^{th} standard and 14 % of patients were studied upto graduate) while only 6 % of them were illiterate. Overall patients had middle socioeconomic status were associated with bipolar disorder. Eid *et al.* 2013 also reported similar distribution of bipolar disorder among socioeconomic classes, educational levels and in a lower family income was reported (Eid *et al.,* 2013). The symptoms of all the patients were assessed at baseline and after 3 weeks of lithium therapy, 68 % and 72 % of patients experienced improvement in symptoms in generic and branded generic groups respectively. In this study the efficacy was assessed using YMRS in both groups. It is a reliable, easy to use, simple and widely used. The YMRS is a valid measurement and 11-item scale used to assess the severity of mania in patients ofbipolar disorder (Kongsakon and Bhatanaprabhabhan, 2005). The mean difference in YMRS from baseline to 2^{nd} follow-up was 14.08 ± 0.70 in generic group and 15.88±0.98 in branded generic group which was similar to study done by Bowden CL *et al.* (2010) who reported mean difference of YMRS was 15.80 ± 0.53 (Bowden *et al.,* 2010). We observed that in both group (generic vs. branded generic) lithium carbonate were effective in context to reduce the YMRS at the 3^{rd} week compared to baseline YMRS. Study done by Machado-Vieira *et al.* (2014) showed that the patients treated with lithium had significantly lower level of YMRS at 3^{rd}& 4^{th} week compared to baseline (Machado-Vieira *et al.,* 2014). However, in our study 32 % of patients in generic group and 28 % of patients in branded generic group persisted with symptoms like dysphoric mood, irritable, verbal abusive and restlessness at 3^{rd} week. Patients need long term therapy for remission stage in bipolar disorder. YMRS score is an average score of all symptoms in patients of bipolar disorder and with improvement of YMRS score, some symptoms may persist even after treatment and treatment for long term helps in improvement of all symptoms.

In generic group, 16 %and in branded generic group, 22 % of patients required concomitant drugs other than lithium therapy (antipsychotic, benzodiazepines) as an augmentation therapy and to control the additional psychotic features other than manic symptoms. Although the concomitant drugs were started within a week as an augmentation therapy, YMRS score was significantly reduced at 3^{rd} week in all patients both by generic and branded generic lithium carbonate. More over in both the group concomitant drugs were required in only few patients without any significant differences between groups. We observed that, at the end of 3 weeks, the mean serum lithium level in generic group was 0.68 (meq/l) and in branded generic group was 0.82 (meq/l) which was similar to study done by Prakash *et al.* (2000) who also observed mean serum lithium level was 0.84 ± 0.18 (meq/l) (Prakash and Bharath, 2000). Although the difference was not statistically significant, the mean serum lithium level in branded generic group was found little higher than in generic group which could be due to the four patients in branded generic group who had high serum lithium level while none of the patients in generic group had high serum lithium level. Even though both formulations contain only one active ingredients as a lithium carbonate and no any other inactive ingredients, absorption of lithium or pharmacokinetics features may vary to person to person or depending on the different formulation used. Furthermore, excipients and inactive ingredients may vary in different formulation, and there is evidence in the literature to suggest that these changes can significantly affect the absorption and different pharmacokinetic properties of drug formulations (Verbeeck *et al.,* 2006). This study shows that those patients who had low level of S. lithium level (< 0.3 meq/L) the improvement in YMRS was lower than the average YMRS of the group and who had high S. lithium level (> 1.2 meq/L) there score also improved equally or a little more than the average score. But at the same time higher S. lithium level was also associated with high incidence of adverse drug reactions such as diarrhoea, lethargy and muscle weakness as compared to average lithium level. Thus, a reasonable therapeutic range for steady state plasma concentration of s. lithium level is necessary for optimal response. However, the evidence for a relation between the steady state standard concentration and a therapeutic effect in the prophylaxis of unipolar and bipolar affective disorder is less clear (Aronson *et al.,* 1992). In study

done by Severus *et al.* suggest that the minimum efficacious serum lithium level in the long-term treatment of bipolar disorder was 0.4 meq/L with optimal response achieved at serum levels between 0.60 to 0.75 meq/L and higher levels may benefit patients with predominantly manic symptoms (Severus *et al.,* 2008). Result of the present study has showed the correlation between plasma lithium level and efficacy of lithium carbonate in patient of bipolar disorder with different formulations. Correlation was done by Pearson Parametric Correlation test in both groups. We found that there was positive correlation between YMRS and plasma lithium level in both groups which means that YMRS score improves when there is an increase in plasma lithium level within therapeutic range which was similar to study done by Nierenberg *et al*. (2013) and Machado-Vieira *et al.,* (2014). A study by Perlis *et al.* did not identify a superior efficacy of using higher lithium levels (≥0.8 mm/l) in long term maintenance therapy (Perlis *et al.,* 2002). In addition branded generic lithium carbonate improved YMRS slightly higher than generic lithium carbonate however there was no statistical significant between two products. Correlation coefficient (r) was found 0.5191 in generic group (P= 0.0474) and 0.5555 in branded generic group (P= 0.0316), hence both different formulations of lithium carbonate shows similar positive correlation between S. lithium level and YMRS means score improves when there is an increase in plasma lithium level. A total, 16 % of patients experienced a common adverse effects such as headache, confusion, polyuria, diarrhoea, lethargy, dry mouth and muscle weakness in bipolar mood disorder subjects in the present study. Study done by Girardi *et al.* (2016) also reported that the total 18 % of patients experienced ADRs who were given immediate release of lithium carbonate. Generally lithium-associated toxicity and adverse events are related to serum concentrations of lithium and normally occur at concentrations> 1.5–2.0 meq/L (Girardi *et al,* 2016).

Therefore, therapeutic drug monitoring is an important part of lithium therapy. In this study, 3 patients in branded generic group experienced adverse effect due to higher level of serum lithium level which suggest that high serum lithium level is associated with toxicity. Also it was observed that these patients were only on lithium with no concomitant therapy which shows that pharmacokinetic variation in patients may be responsible for these ADRs. Study done by Kemp DE *et al.* reported that 10%of patients discontinued the study during the open-label phase because of adverse events, (Kemp *et al.,* 2009) while in our study no dropouts were observed due to adverse events during lithium therapy upto 3 weeks. However out of 8,3 patients developed polyuria and diarrhoea and required dose reduction of lithium therapy from 300 mg thrice a day to 300 mg twice a day. Out of 8 ADRs, 5 ADRs were assessed as probable and 3 ADRs were assessed as possible causality assessment in both groups. Most of the adverse events reported in this study were considered to be mild except 1 ADR which was considered as moderate and resolved without sequelae. Hence, a correlation of serum lithium level and ADRs can help to find out whether the differences between generic and branded generic is due to pharmacokinetic variations. This study highlights that there is significant mean reduction in YMRS score in both group and shows similar efficacy in bipolar disorder, but it was observed that 3 patients were found with high S. lithium level in branded generic group. Borgheini *et al.* observed plasma levels of phenytoin were 31% lower after a switch from a brand-name to a generic product (Borgheini, 2016). Samuel *et al.* (2013) reported a case of 14 year boy with an acute clinical deterioration within 48 hours when branded olanzapine changed to generic olanzapine (Samuel *et al.,* 2013). Hence, in many instances bioavailability, therapeutic efficacy and tolerability may vary between brand-name and generic drugs. Most generic drugs are marketed after they have passed the bioequivalence tests under standard licensingagencies like FDA and BA/BE studies are also required for certain drugs who have narrow therapeutic index to ensure therapeutic equivalence between test product and reference product in India. The objective of a typical bioequivalence study is to demonstrate that the test (reference) and reference (branded) products achieve a similar pharmacokinetic profile in plasma, serum and/or urine (Samuel *et al.,* 2013). Generic medicines are as good as branded medicines with regard to bioequivalence and therapeutic equivalence if generic products that have passed through quality assurance programs, including those manufactured in plants that have a Good Manufacturing Practice certification (Alfonso Cristancho *et al.,* 2015). Clinical evidence suggests that differences between most branded and generic drugs are negligible (Kesselheim *et al.,* 2008). But the problem is fake medicines, inadequate/excess content of active ingredients, presence of impurities or both can be curtailed using strict quality control methods to make drugs available at affordable price (Meredith *et al.,* 2003). Present study also shows that optimal S. lithium level is associated with improvement in YMRS. Hence there is strong correlation between efficacy (YMRS) and serum lithium level of two different formulations. Therapeutic drug monitoring of S. lithium level is important to establish dose response relationship. We conclude that doses resulting in serum lithium levels in normal therapeutic range are more effective in treating bipolar disorder than those that result in lower serum lithium concentrations, or even higher S. lithium level are associated with a higher incidence of side effects. There are few limitation of the study. In our study, small number of patients were enrolled as we included only new patients on lithium therapy. We allowed benzodiazepines or antipsychotics drugs in this study as an augmentation therapy which could have some effects in reducing manic symptoms.

Conclusion

This study is a landmark study which has shown that generic and branded generic are equally efficacious. However a monitoring of serum lithium level at regular interval can help to prevent ADR due to pharmacokinetic variation.

Acknowledgements: I am extremely thankful to Dr. Chauhan sir, Superintendent of Mental hospital, Delhi Darwaja, Ahmedabad for granting me the permission to conduct the study. Also thankful to all the staff and patients of bipolar disorder for their co-operation during study without whom it was impossible to do this research work.

Conflict of interest: There is no conflict of interest.

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